PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2004/006562	International filing date *(day/month/year)* 17.06.2004
Priority date *(day/month/year)* 18.06.2003	
International Patent Classification (IPC) or both national classification and IPC A61K31/553, A61P37/08, A61P27/14	
Applicant NOVARTIS AG	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Authorized Officer

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 6,7, 11, 12-16,19 (IA)

because:

☒ the said international application, or the said claims Nos. 6,7, 11, 12-16,19 (IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 6,7, 11, 12-16,19 (IA)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-19

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3, 4, 5, 7, 8, 11, 13, 14, 15, 16, 17, 18, 19
	No:	Claims	1,2,6,10
Inventive step (IS)	Yes:	Claims	4, 5, 7, 9, 12
	No:	Claims	1-3, 6, 8, 10, 11, 13, 14, 15, 16, 17, 18, 19
Industrial applicability (IA)	Yes:	Claims	1, 2, 3, 8, 10, 17, 18
	No:	Claims	

2. Citations and explanations

   see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/006562

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

The following document have been cited in the search report. Where reference is made to them, the following numbering is used; unless otherwise indicated, reference is made to the relevant passages emphasized in the Search Report:

D1: WO 97/49406 A (CEPHALON INC (US);31 December 1997

D2: WO03065995

D3: WO 99/62537 A (CORNELL RES FOUNDATION INC) 9 December 1999

D4: WO 98/48795 A (LILLY CO ELI) 5 November 1998 (1998-11-05)

D5: DATABASE WPI Section Ch, Week 198903 Derwent Publications Ltd., London, GB; Class B02, AN 1989-019684 XP002295579 & JP 63 295589 A (KYOWA HAKKO KOGYO KK) 1 December 1988

D6: WO 02/46197 A (ORTHO MCNEIL PHARM INC) 13 June 2002

D7: EP-A-0 470 490 (HOFFMANN LA ROCHE) 12 February 1992

D8: AMON U ET AL: "CGP 41251, a novel protein kinase inhibitor with in vitro selectivity for protein kinase C, strongly inhibits immunological activation of human skin mast cells and human basophils." PHARMACOLOGY. SEP 1993, vol. 47, no. 3, September 1993, pages 200-208, XP009036185

D9: KUROSAWA M ET AL: "Effect of staurosporine on histamine release from rat serosal mast cells." ANNALS OF ALLERGY. SEP 1989, vol. 63, no. 3, September 1989, pages 231-234, XP009036192

D10: WO03037347

D11: WO 02/080925 A (NOVARTIS AG 17 October 2002

D12: OPDAL S H ET AL: "New insight into sudden infant-death syndrome" LANCET THE, LANCET LIMITED. LONDON, GB, vol. 364, no. 9437, (2004-09-04), pages 825-826, XP004552551

D13: US-A-4 639 455 (MOORE LUANA) 27 January 1987 (1987-01-27)

D14: EP-A-0 518 468 (NEURIM PHARMA 1991) 16 December 1992 (1992-12-16)

D15: WARK P A ET AL: "Allergic bronchopulmonary aspergillosis: new concepts of pathogenesis and treatment." RESPIROLOGY (CARLTON, VIC.) MAR 2001, vol. 6, no. 1, pages 1-7, XP002313470

D16: GREENBERGER PAUL A: "Clinical aspects of allergic bronchopulmonary aspergillosis." FRONTIERS IN BIOSCIENCE : A JOURNAL AND VIRTUAL LIBRARY. 1 JAN 2003, vol. 8, 1 January 2003, pages s119-s127, XP002313471

D17: SVIRSHCHEVSKAYA E V ET AL: "Immunotherapy of allergic bronchopulmonary aspergillosis: a clinical and experimental approach." FRONTIERS IN BIOSCIENCE : A JOURNAL AND VIRTUAL LIBRARY. 1 JAN 2003, vol. 8, 1 January 2003, pages s92-101, XP002313472 ISSN: 1093-4715

D18: WO 96/31514 A (SANDOZ LTD) 10 October 1996

D19: BRADSHAW D ET AL: "THERAPEUTIC POTENTIAL OF PROTEIN KINASE C INHIBITORS" AGENTS AND ACTIONS, BIRKHAEUSER VERLAG, vol. 38, 1993, pages 135-147, XP009034964

D20: HUDSON S J ET AL: "Intracellular signaling of tumor necrosis factor-alpha in brain microvascular endothelial cells is mediated by a protein tyrosine kinase and protein kinase C-dependent pathway." JOURNAL OF NEUROIMMUNOLOGY. NOV 1996, vol. 70, no. 2, pages 199-206, XP002313473

D21: JUREWICZ A M ET AL: "Shedding of TNF receptors in multiple sclerosis patients." NEUROLOGY. 22 OCT 1999, vol. 53, no. 7, 22 October 1999 (1999-10-22), pages 1409-1414, XP008041519

D22: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MORISHITA,

TSUYOSHI ET AL: "Drug for nerve regeneration containing glycogen synthase kinase-3 inhibitors" XP002313532 retrieved from STN Database accession no. 2004:902218

D23: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; KITA, YASUHIRO ET AL: "Remedy for cerebral neurodegenerative diseases using PPAR.delta. agonist" XP002313533 retrieved from STN Database accession no. 2004:927076

D24: LONGLEY B J ET AL: "NEW APPROACHES TO THERAPY FOR MASTOCYTOSIS A CASE FOR TREATMENT WITH KIT KINASE INHIBITORS" HEMATOLOGY - ONCOLOGY CLINICS OF NORTH AMERICA, W.B. SAUNDERS, US, vol. 14(3), June 2000, pages 689-695, XP008010967

D25: THARP M D: "Mastocytosis" CURRENT PROBLEMS IN DERMATOLOGY 1998 UNITED STATES, vol. 10, no. 5, 1998, pages 181-210, XP009030211 ISSN: 1040-0486

Re Item III.

Non establishment of opinion with regard to novelty, inventive step, industrial application.

For the assessment of the present claims 6, 7, 11, 12-16, 19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item IV.

Lack of unity of invention.

The ISA has found that the application does not meet the PCT requirement of unity of invention. The reasoning for this finding and the inventions which have been identified are indicated below.

INVENTION 1: Claims : 1, 2, 3, 6, 8, 10, 11, 13, 14, 15, 16, 17 ,18 ,19 (partial);

Use of compounds falling in the Markush definition (A) of claim 1 and of formula (I), (II), (III), (VI) of claim 2 in relation to the treatment of allergic rhinitis, allergic dermatitis, drug or food allergy, angioderma and urticaria.

INVENTION 2: Claims : 1, 2, 3, 6, 8, 10, 11, 13, 14, 15, 16, 17 ,18 ,19 (partial);

Use of compounds falling in the Markush definition (A) of claim 1 and of formula (I), (II), (III), (VI) of claim 2 in relation to the treatment of sudden infant death syndrome.

INVENTION 3: Claims : 1, 2, 3, 6, 8, 10, 11, 13, 14, 15, 16, 17 ,18 ,19 (partial);

Use of compounds falling in the Markush definition (A) of claim 1 and of formula (I), (II), (III), (VI) of claim 2 in relation to the treatment of bronchopulmonary aspergillosis.

INVENTION 4: Claims : 1, 2, 3, 6, 8, 10, 11, 13, 14, 15, 16, 17 ,18 ,19 (partial);

Use of compounds falling in the Markush definition (A) of claim 1 and of formula (I), (II), (III), (VI) of claim 2 in relation to the treatment of multiple sclerosis.

INVENTION 5: Claims : 1, 2, 3,4,5 6,7, 8, 10, 11, 13, 14, 15, 16, 17 ,18 ,19 (partial); 9, 12, (complete)

Use of compounds falling in the Markush definition (A) of claim 1 and of formula (I), (II), (III), (VI) of claim 2 in relation to the treatment of mastocytosis.

INVENTION 6: Claims : 1, 2, 6, 19 (partial);

Use of compounds falling in the Markush definition (B) and (C) of claim 1 and of formula (V) of claim 2 in relation to the treatment of allergic rhinitis, allergic dermatitis, drug or food allergy, angioderma and urticaria.

INVENTION 7: Claims : 1, 2, 6, 19 (partial);

Use of compounds falling in the Markush definition (B) and (C) of claim 1 and of formula (V) of claim 2 in relation to the treatment of sudden infant death syndrome.

INVENTION 8: Claims : 1, 2, 6, 19 (partial);

Use of compounds falling in the Markush definition (B) and (C) of claim 1 and of formula (V) of claim 2 in relation to the treatment of bronchopulmonary aspergillosis.

INVENTION 9: Claims : 1, 2, 6, 19 (partial);

Use of compounds falling in the Markush definition (B) and (C) of claim 1 and of formula (V) of claim 2 in relation to the treatment of multiple sclerosis.

INVENTION 10: Claims : 1, 2, 4, 5, 6,7, 19 (partial);

Use of compounds falling in the Markush definition (B) and (C) of claim 1 and of formula (V) of claim 2 in relation to the treatment of mastocytosis.

INVENTION 11: Claims : 1, 2, 3, 6, 8, 10, 11, 13, 14, 15, 16, 17 ,18 ,19 (partial);

Use of compounds falling in the Markush definition (D) of claim 1 and of formula (IV) of claim 2 in relation to the treatment of allergic rhinitis, allergic dermatitis, drug or food allergy, angioderma and urticaria.

INVENTION 12: Claims : 1, 2, 3, 6, 8, 10, 11, 13, 14, 15, 16, 17 ,18 ,19 (partial);

Use of compounds falling in the Markush definition (D) of claim 1 and of formula (IV) of claim 2 in relation to the treatment of sudden infant death syndrome.

INVENTION 13: Claims : 1, 2, 3, 6, 8, 10, 11, 13, 14, 15, 16, 17 ,18 ,19 (partial);

Use of compounds falling in the Markush definition (D) of claim 1 and of formula (IV) of claim 2 in relation to the treatment of bronchopulmonary aspergillosis.

INVENTION 14: Claims : 1, 2, 3, 6, 8, 10, 11, 13, 14, 15, 16, 17 ,18 ,19 (partial);

Use of compounds falling in the Markush definition (D) of claim 1 and of formula (IV) of claim 2 in relation to the treatment of multiple sclerosis.

INVENTION 15: Claims : 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 13, 14, 15, 16, 17 ,18 ,19 (partial);

Use of compounds falling in the Markush definition (D) of claim 1 and of formula (IV) of claim 2 in relation to the treatment of mastocytosis.

Reasons

The problem underlying the present application is the provision of compositions for the treatment of the following diseases: allergic rhinitis, allergic dermatitis, drug and food allergy, angioderma, urticaria, sudden infant death syndrome, bronchopulmonary aspergillosis, multiple sclerosis, mastocytosis.

To solve this problem the inventors propose compositions comprising staurosporin derivatives having different structural features. In particular the inventors propose the use of compounds having the formula A-C (as shown in claim 1), or having formula I-VI as shown in claim 2.

Rule 13.1 PCT deals with the requirement of unity of invention, and states the principle that an international application should relate to only one invention or, if there is more than one invention, that the inclusion of those inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept. Rule 13.2 PCT defines the method for determining whether the requirement of unity of invention is satisfied in respect of a group of inventions claimed in an international application. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features." The expression "special technical features" is defined in Rule 13.2, as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art.

The problem underlying the present application has found similar solutions in the prior art; reference is made to the documents listed above, and in particular to the passages which are cited in the search report:

D1 discloses the use of compounds falling under the Markush formula A of claim 1 and

under formula III of claim 2 for the treatment of allergic rhinitis, dermatitis and other allergic diseases.
D3 discloses the use of staurosprorine derivatives (falling in the Markush formula (A) of claim 1 and in the formula(I) of claim 2), for the treatment of immunitary responses; food allergy, allergic rhinitis, allergic conjunctivitis are also mentioned.
D4 discloses the use of compounds falling in the definition of the Markush formula (A) of claim 1 and in the formula V of claim 2 for the treatment of contact dermatitis and other allergic disorders.
D5 and D6 disclose the use of compounds falling under the Markush formula A of claim 1 and under formula III of claim 2 for the treatment of allergic disorders.
D7 discloses the use of compounds falling into the definition of the Markush formula (D) of claim 1 and of formula (IV) of claim 2 for the treatment of contact dermatitis and other allergic diseases.
D10 discloses the use of all the preferred compounds claimed in the present application for the treatment of leukemia.

It is clear from the above mentioned prior art that the use of staurosporine derivatives of different types, falling among the preferred compounds defined by the Markush shown in claims 1 and 2 of the present application has been already disclosed for the treatment of a number of the conditions claimed in the present application (in particular for the treatment of allergic diseases).

In view of the above mentioned prior art, in the present application no further technical feature(s) can be distinguished that can be regarded as a "special technical feature" involved in the technical relationship among the different inventions. Consequently, the present application lacks unity of invention; the different solutions not belonging to a common inventive concept are identified as the different subjects listed above. Each of the inventions listed above is a distinct invention, characterised by its own special technical feature, defining the contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

After being invited to pay additional search fees, the applicant has paid four additional fees for inventions 4-5 respectively. These inventions have been searched, and will be the subject of the following opinion from the WO-ISA.

Re Item V.

Reasoned statement on novelty, inventive step and industrial application.

OPINION ON INVENTION N.1

NOVELTY (Art.33(2) PCT)

D1 discloses the use of compounds falling under the Markush formula A of claim 1 and under formula III of claim 2 for the treatment of allergic rhinitis, dermatitis and other allergic diseases.
D3 discloses the use of staurosprorine derivatives (falling in the Markush formula (A) of claim 1 and in the formula(I) of claim 2), for the treatment of immunitary responses; food allergy, allergic rhinitis, allergic conjunctivitis are also mentioned.

In view of this prior art the subject matter of claims 1, 2, 6, is not new in the sense of Art.33(2) PCT.

D10 discloses the use of all the preferred compounds claimed in the present application for the treatment of leukemia. Claim 10, which is directed to a pharmaceutical composition comprising PKC412 is not new over this prior art. The intended use indicated in this claim is irrelevant for the assessment of novelty of this claim.

INVENTIVE STEP Art.33(3) PCT

The problem underlying the first invention of the present application is the provision of a medicament for the treatment of the following allergic conditions: rhinitis, allergic dermatitis, drug or food allergy, angioderma and urticaria. All these conditions are known to involve histamine release by mast cells and are treated with antihistamine agents.
As a solution the applicants provide compounds falling in the definition of formula (A) in claim 1 and in formula (I, II, III, VI) of claim 2.
D1 and **D3** mentioned above show that compounds falling among the compounds of formula A have already been used to treat some of these conditions.

The subject matter which is still new differs from the prior art in that some related compounds have been used (the ones falling in the definition of formula (I, II, VI for example), the preferred compound being PKC412 (staurosporine). This preferred compound is however known to inhibit the release of histamine from mast cells (see **D8** and **D9**). In view of this prior art, a skilled person would therefore expect also staurosporine and its derivatives to be active for the treatment of the allergic conditions listed above. In view of this prior art, the subject matter of the first invention which is still new, is not considered to involve an inventive step in the sense of Art.33(3) PCT.

INDUSTRIAL APPLICATION

Claims 6, 7, 11, 12-16, 19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT). The other claims are industrially applicable.

OPINION ON INVENTION N.2

NOVELTY (Art.33(2)) PCT

No one of the prior art documents discloses the use of compounds as claimed in the formula (A) in claim 1 and in formula (I, II, III, VI) of claim 2 for the treatment of infant death syndrome. The subject matter defined in the second invention is therefore new in the sense of Art.33(2) PCT.

INVENTIVE STEP (Art.33(3) PCT)

The problem underlying the second invention is the provision of a medicament for the treatment of infant death syndrome. No one of the prior art documents would prompt a skilled person to use staurosporine derivatives as claimed in the present application for the treatment of infant death syndrome. Even if some compounds have been proposed to treat this disease, no one of them mentions or refers to staurosporines (see in particular D11-D14).
However, in the present application no evidence is shown that the problem underlying the

invention has been solved. The inventors report in the description that the staurosporine "compound I" inhibits the activation of kit kinase associated with canine mast cell tumors and inhibits the proliferation of cell lines of canine mast cell tumors. These experimental results however are not a credible evidence that this effect on mast cells will prevent infant death syndrome.
For these reasons, in the absence of an unambiguous evidence that the problem underlying the invention has been solved, the subject matter of claims 1-3,6,8,11,19 which relates to the second invention may not be considered to involve an inventive step in the sense of Art.33(3) PCT.

INDUSTRIAL APPLICATION

Claims 6, 7, 11, 12-16, 19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT). The other claims are industrially applicable.

OPINION ON INVENTION N.3

NOVELTY (Art.33(2) PCT)

No one of the prior art documents discloses the use of compounds as claimed in the formula (A) in claim 1 and in formula (I, II, III, VI) of claim 2 for the treatment of bronchopulmonary aspergillosis. The subject matter defined in the third invention is therefore new in the sense of Art.33(2) PCT.

INVENTIVE STEP (Art.33(3) PCT)

The problem underlying the third invention is the provision of a medicament for the treatment of bronchopulmonary aspergillosis. No one of the prior art documents would prompt a skilled person to use staurosporine derivatives as claimed in the present application for the treatment of bronchopulmonary aspergillosis. Even if some compounds have been proposed to treat this disease, no one of them mentions or refers to staurosporines (see in particular D15-D18).

However, in the present application no evidence is shown that the problem underlying the invention has been solved. The inventors report in the description that the staurosporine "compound I" inhibits the activation of kit kinase associated with canine mast cell tumors and inhibits the proliferation of cell lines of canine mast cell tumors. These experimental results however are not a credible evidence that this effect on mast cells will prevent infant death syndrome.
For these reasons, in the absence of an unambiguous evidence that the problem underlying the invention has been solved, the subject matter of claims 1-3,6,8,11,19 which relates to the second invention may not be considered to involve an inventive step in the sense of Art.33(3) PCT.

INDUSTRIAL APPLICATION

Claims 6, 7, 11, 12-16, 19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT). The other claims are industrially applicable.

OPINION ON INVENTION N.4

NOVELTY (Art.33(2)) PCT

No one of the prior art documents discloses the use of compounds as claimed in the formula (A) in claim 1 and in formula (I, II, III, VI) of claim 2 for the treatment of multiple sclerosis. The subject matter defined in the fourth invention is therefore new in the sense of Art.33(2) PCT.

INVENTIVE STEP (Art.33(3) PCT)

The problem underlying the fourth invention is the provision of a medicament for the treatment of infant death syndrome. No one of the prior art documents would prompt a skilled person to use staurosporine derivatives as claimed in the present application for the treatment of infant death syndrome. D19 mentions the possibility to use protein kinase C inhibitors to treat multiple sclerosis. This document refers to staurosporine as a protein

kinase C inhibitor, but also explains that this compound, due to its scarce selectivity is not suitable. Also the other documents D20-D21 which refer to staurosporine derivatives, would not prompt a skilled person to use these compounds for the treatment of multiple sclerosis.
However, in the present application no evidence is shown that the problem underlying the invention has been solved. The inventors report in the description that the staurosporine "compound I" inhibits the activation of kit kinase associated with canine mast cell tumors and inhibits the proliferation of cell lines of canine mast cell tumors. These experimental results however are not a credible evidence that this effect on mast cells will prevent infant death syndrome.
For these reasons, in the absence of an unambiguous evidence that the problem underlying the invention has been solved, the subject matter of claims 1-3,6,8,11,19 which relates to the second invention may not be considered to involve an inventive step in the sense of Art.33(3) PCT.

INDUSTRIAL APPLICATION

Claims 6, 7, 11, 12-16, 19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT). The other claims are industrially applicable.

OPINION ON INVENTION N.5

NOVELTY (Art.33(2)) PCT

No one of the prior art documents discloses the use of compounds as claimed in the formula (A) in claim 1 and in formula (I, II, III, VI) of claim 2 for the treatment of mastocytosis. The subject matter defined in the fifth invention is therefore new in the sense of Art.33(2) PCT.

INVENTIVE STEP (Art.33(3) PCT)

The problem underlying the fifth invention is the provision of a medicament for the

treatment of infant death syndrome. No one of the prior art documents would prompt a skilled person to use staurosporine derivatives as claimed in the present application for the treatment of mastocytosis.
The inventors have shown in the description of the present application that the staurosporine "compound I" inhibits the activation of kit kinase associated with canine mast cell tumors and inhibits the proliferation of cell lines of canine mast cell tumors.
This evidence appears to indicate that the compounds claimed in the present application will be useful to treat or prevent mastocytosis, and that the problem underlying the invention has been solved. The subject matter of claims 1-19 relating to the fifth invention appears therefore to involve an inventive step in the sense of Art.33(3) PCT.

INDUSTRIAL APPLICATION

Claims 6, 7, 11, 12-16, 19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT). The other claims are industrially applicable.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO03065995	14 /08/ 2003	6/ 02/ 2003	7/ 02/ 02
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These documents, which were filed before the priority date of the present application could become relevant in the procedure before the designated / elected national authorities.